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The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure

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Mortality reports on asbestos exposed cohorts which gave information on exposure levels from which (as a minimum) a cohort average cumulative exposure could be estimated were reviewed. At exposure levels seen in occupational cohorts it is concluded that the exposure specific risk of mesothelioma from the three principal commercial asbestos types is broadly in the ratio 1:100:500 for chrysotile, amosite and crocidolite respectively. For lung cancer the conclusions are less clear cut. Cohorts exposed only to crocidolite or amosite record similar exposure specific risk levels (around 5% excess lung cancer per f/ml.yr); but chrysotile exposed cohorts show a less consistent picture, with a clear discrepancy between the mortality experience of a cohort of chrysotile textile workers in Carolina and the Quebec miners cohort. Taking account of the excess risk recorded by cohorts with mixed fibre exposures (generally<1%), the Carolina experience looks uptypically high. It is suggested that a best estimate lung cancer risk for chrysotile alone would be 0.1%, with a highest reasonable estimate of 0.5%. The risk differential between chrysotile and the two amphibole fibres for lung cancer is thus between 1:10 and 1:50.

Examination of the inter-study dose response relationship for the amphibole fibres suggests a non-linear relationship for all three cancer endpoints (pleural and peritoneal mesotheliomas, and lung cancer). The peritoneal mesothelioma risk is proportional to the square of cumulative exposure, lung cancer risk lies between a linear and square relationship and pleural mesothelioma seems to rise less than linearly with cumulative dose. Although these non-linear relationships provide a best fit to the data, statistical and other uncertainties mean that a linear relationship remains arguable for pleural and lung tumours (but not for peritoneal tumours).

Based on these considerations, and a discussion of the associated uncertainties, a series of quantified risk summary statements for different levels of cumulative exposure are presented.

Keywords: asbestos; amphibole hypothesis; exposure-response; lung cancer; mesothelioma; quantified risk assessment

INTRODUCTION

There has been much debate on the relative hazardousness of the three main asbestos types: crocidolite, amosite and chrysotile (commonly known as blue, brown and white asbestos respectively), but no systematic attempt to quantify the differences. Existing published quantitative risk assessments have mostly not distinguished between the fibre types, and none has produced quantified estimates of the risk from amphiboles (a collective mineralogical term covering crocidolite and amosite). A review commissioned by the HSE in the 1980s from Professors Richard Doll and Julian Peto (1985) gave estimates for chrysotile alone; more recently a review by the Health Effects Institute (1991) produced estimates for an unspecified mixture of fibre types. An INSERM review (1996) also ignored differences in fibre type, and drew heavily on the HEI review.

The studies included in this review were selected by reviewing the material referenced in the Doll and Peto, HEI and INSERM reports and identifying all cohort mortality reports for which quantified data on

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ers hired before 1940, which conflicts with the period of known use of crocidolite yarn (in very small quantities—see Appendix A) in the plant after 1950. This raises the possibility that some amphibole formed part of the exposure mix in this cohort in an early period. Green *et al.* (1997) show that the levels of amphibole are higher in Carolina workers than in local controls (2-fold difference in geometric mean, P=0.031) but much less strikingly than for chrysotile (5-fold, P<0.0001) or tremolite (14-fold, P<0.0001). They also report that amphibole at levels >1.0 f/μg (all fibre lengths) were found in only one of the ten lung cancer cases for whom this datum was available. This last observation limits the extent to which amphibole exposure—perhaps unrecognised—might play a role in this cohort. Whatever mechanism is in play does not appear to apply—to the same extent, at least—to the other two textile cohorts reviewed. As already pointed out, the Pennsylvania and Rochdale cohorts (with mixed fibre exposures) both give substantially lower estimates of R_L.

If it is accepted that some such feature of the processing in the Carolina cohort has genuinely produced a much higher risk than seen in other chrysotile cohorts the question can be asked how typical these features are of the bulk of applications? Looked at in the wider context of cohorts with mixed fibre exposure, the R_L value for Carolina looks untypically high. Setting aside the possibility that amphibole presents a higher risk of lung cancer, the observations of R_L from mixed fibre cohorts can be taken as informative of the R_L level for chrysotile. This suggests that in typical applications (including other textile processes) R_L for chrysotile is generally lower than the value derived from the Carolina cohort. The median R_L for the 16 cohorts with some chrysotile exposure is 0.5, compared to 4.5 for Carolina men and 6.7 for Carolina women. All but two of the mixed fibre cohorts give an R_L estimate less than 1, and of the two exceptions one (Albin) has a confidence limit including zero, and the other (Ontario) shows features suggestive of significant exposure to crocidolite (see below, Fig. 4 and related text).

To the extent that amphibole fibres make a disproportionate contribution to the lung cancer risk in the mixed exposure cohorts—and the evidence presented here suggests that they do—the typical risk of lung cancer from chrysotile exposure would be even lower. In most circumstances a value of 0.5% per f/ml.yr should probably be regarded as an upper limit to the lung cancer risk from pure (commercial) chrysotile. The mean R_L estimate for mixed fibre cohorts excluding the three with particular interpretational difficulties is 0.32% per f/ml.yr with an upper 95% confidence limit of 0.50.

It should be noted that a value of 0.5% per f/ml.yr is not as far out of line with the Carolina observations as it might seem. The 'cohort average' risk estimate from this cohort (6.7 for women, 4.7 for men) probably overestimates the risk, which from internal analysis is 1 for women and 3 for men (Dement *et al.*, 1994, p. 439). The exposure response regressions on this cohort give an intercept close to zero excess risk at zero dose, and there is thus no reason to suspect serious error in the reference rates (with consequential doubts about interpreting the slope). There is also the possibility of inaccuracies in the conversion of particle counts to fibre counts. One early report on this cohort (McDonald *et al.*, 1983a) suggested that the average conversion factor should be about 6 f/ml to 1 mppcf. If this were true, the risk per f/ml.yr would be halved.

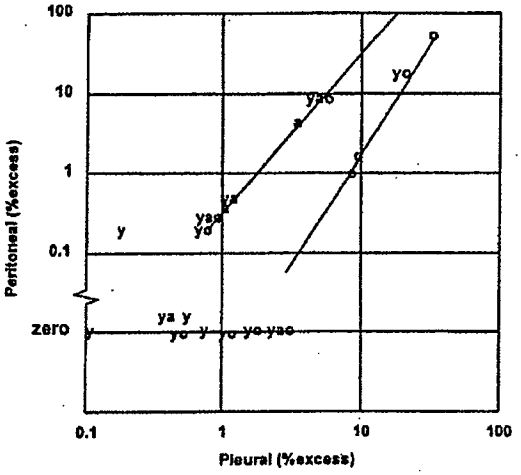

Fig. 4. Comparison of excess mortality from pleural and peritoneal mesothelioma, showing fibre type.

A 'best estimate' of the lung cancer risk would be lower than 0.5% per f/ml.yr. Noting that the mean risk of the mixed fibre cohorts (excluding the three mentioned above) is 0.32% per f/ml.yr, and that the amphibole risk is over 10 times higher, it is possible that virtually all the observed risk could be explained by rather less than 10% of amphibole in the mixed exposures. However there is no direct evidence on which an estimate of the risk of 'pure' chrysotile could be based. Apart from the Balangero cohort, all the chrysotile evidence considered here effectively relates to Canadian chrysotile, since this was the dominant source of fibre for the other chrysotile cohorts. The risk of 'commercial' chrysotile as estimated from the mining cohorts is 0.06% per f/ml.yr. Given that the processing of chrysotile may produce some additional risk, the best estimate should be set higher than the mines level, say at 0.1% per f/ml.yr. The overall risk, of a mixture of 96% chrysotile with a risk of 0.1, and 4% amphibole with a risk of 5.1 would be 0.3% per f/ml.yr.

EXTRAPOLATION TO LOW EXPOSURES

All these cohort observations reflect the effect of exposure to high levels of asbestos. The main interest

in quantitative risk assessment in current conditions is to apply this evidence to the estimation of the risks associated with exposure levels 100–1000 times lower. The standard assumption is that, other things being equal, the risk will be proportional to dose; but this is more a cautious default assumption than anything more soundly based. To quote from the HEI review: "The assumption of dose-linearity for low-dose assessment purposes is thus a widely accepted and scientifically reasonable compromise rather than an established scientific principle of carcinogenesis".

However, if the true relationship between exposure and response was not linear, the impact on low dose extrapolations could be dramatic. There is some indication in the present data suggesting a non-linear exposure response, particularly for peritoneal mesothelioma, and the next sections examine this question.

Relationship of pleural and peritoneal mesothelioma

Figure 4 plots the percentage excess mortality from peritoneal mesothelioma against that from pleural mesothelioma. Cohorts with no mesothelioma cases of either kind are excluded. Cohorts with no peritoneal mesotheliomas are plotted on the peritoneal scale on or close to the 0.01 ordinate. The positioning of the cohort points strongly suggests a pattern of two alignments, one defined by the pure crocidolite cohorts, the other by the two pure amosite cohorts. Four mixed exposure cohorts lie very close to the amosite line: the US/Canada Insulators, New Orleans plant 1, the Johns Manville retirees and the Albin cohorts. All but the last of these clearly had amosite as the main amphibole fibre. The point representing the Ontario cohort lies very close to the crocidolite line, suggesting perhaps that the anomalous results from this cohort may be explained by underestimated exposure to crocidolite.

The position of the (male) Carolina cohort seems somewhat anomalous. The single peritoneal mesothelioma in this group is the only one in a cohort without material amphibole exposure, and the equality between pleural and peritoneal numbers (one of each) is only otherwise seen in cohorts with much higher levels of mesothelioma (and substantial amphibole exposure). The possibility of unrecognised amphibole exposure again suggests itself, but too much should not be read into this single peritoneal case. It is clear that the three fibre types produce different mesothelioma responses overall. The question of differential responses by mesothelioma site can really only be addressed for the amphibole fibres.

This relationship does not depend on quantified exposure data, and if it is real it should be reproduced in other cohorts with predominant amphibole exposure. The most informative cohorts will be those with crocidolite or amosite exposure, but not both. A Medline search identified eight such cohorts. The relevant data are summarised in Table 3, and a plot of the percent excess mortalities from these cohorts (and the pure fibre quantified cohorts) is shown in Fig. 5.

There is still an apparent separation between crocidolite and amosite cohorts, though the segregation is now less clear cut (as might be expected given the small numbers often involved). There is, of course considerable statistical uncertainty in both of these variables, and a simple regression (in which uncertainty about 'x' values is ignored) would be misleading. Table 4 summarises the results of regressions in which the fit is optimised in both variables simultaneously (fit being measured by deviance, assuming Poisson variation for the numbers of mesotheliomas at each site).

Fitting a single line through all the data produces a line with a slope (on the log–log scale) of 1.2, but the overall fit is unsatisfactory ($P<0.001$). Allowing the two fibres to have separate fits makes a very significant improvement to the fit ($P<0.001$), and both fits have steeper slopes (2.3 for crocidolite and 3.1 for amosite — not shown in table). These slopes are not very precisely determined, and constraining them to be equal does not materially degrade the fit ($P=0.75$). The central estimate for this common slope is 2.4.

This model provides a very close statistical fit to all but two of the cohorts. The two exceptions are the gas mask cohorts in Canada (McDonald and McDonald, 1978) and in Leyland (Acheson *et al.*, 1982), which contribute 6.1 and 4.5 respectively to the total deviance. Possible reasons for these cohorts to be untypical can be identified. The Leyland cohort was not ascertained from employment records, but from occupational details recorded on the wartime population register compiled in September 1939. If the numbers directly involved with gas mask assembly have been over estimated the percentage excess mortalities will be proportionately under estimated. If, for example, only 2/3rds of the identified women were in fact exposed, the expected mortality denominator would fall to around 120, and the residual falls from 6.1 to 4.3—still an outlier, but materially less extreme ($P=0.038$ instead of 0.014). The overall excess mortality from mesothelioma recorded in the Leyland cohort is much lower than in the Nottingham cohort engaged on the same process: 2.7% at Leyland and 16.5% at Nottingham, again suggesting the possibility of underestimation (eg by dilution of the exposed population), perhaps substantial.

The assessment of mesothelioma in the Canadian gas mask cohort was particularly exhaustive, involving review of pathological data for all cancer cases. Three of the six peritoneal cases were only identified after this review. If the number of peritoneal mesotheliomas is reduced by three, the residual for this cohort falls from 4.5 ($P=0.034$) to 2.0 ($P=0.16$).

However these are post-hoc rationalisations, and it is not clear whether it is better to remove these cohorts from the model or not. Despite the large